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Patrizio Lancellotti, Julien Magne, Erwan Donal, Kim O'Connor, Raluca Dulgheru, et al.. Determinants and prognostic significance of exercise pulmonary hypertension in asymptomatic severe aortic stenosis.. *Circulation*, 2012, 126 (7), pp.851-9. 10.1161/CIRCULATIONAHA.111.088427 . hal-00880189

**HAL Id: hal-00880189**

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Submitted on 5 May 2014

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*Circulation*. 2012;126:851-859; originally published online July 25, 2012;  
doi: 10.1161/CIRCULATIONAHA.111.088427

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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## Determinants and Prognostic Significance of Exercise Pulmonary Hypertension in Asymptomatic Severe Aortic Stenosis

Patrizio Lancellotti, MD, PhD\*; Julien Magne, PhD\*; Erwan Donal, MD, PhD; Kim O'Connor, MD; Raluca Dulgheru, MD; Monica Rosca, MD; Luc A. Pierard, MD, PhD

**Background**—Recent studies emphasized the usefulness of exercise stress echocardiography in asymptomatic patients with aortic stenosis. Nevertheless, the additive value of exercise pulmonary hypertension (Ex-PHT) in such patients remains unexplored. We therefore aimed to identify the determinants and to test the impact on outcome of Ex-PHT in asymptomatic patients with severe aortic stenosis.

**Method and Results**—Asymptomatic patients with severe aortic stenosis ( $n=105$ ; aortic valve area  $<0.6$  cm<sup>2</sup>/m<sup>2</sup>; age,  $71\pm 9$  years; male, 59%) and preserved left ventricular systolic function (ejection fraction  $\geq 55\%$ ) were prospectively submitted to exercise stress echocardiography. Resting PHT and Ex-PHT were defined as a systolic pulmonary arterial pressure  $>50$  and  $>60$  mm Hg, respectively. Ex-PHT was more frequent than resting PHT (55% versus 6%;  $P<0.0001$ ). On multivariable logistic regression, the independent predictors of Ex-PHT were male sex (odds ratio, 4.3;  $P=0.002$ ), resting systolic pulmonary arterial pressure (odds ratio, 1.16;  $P=0.002$ ), exercise indexed left ventricular end-diastolic volume (odds ratio, 1.04;  $P=0.026$ ), exercise  $e'$ -wave velocity (odds ratio, 1.35;  $P=0.047$ ), and exercise-induced changes in indexed left atrial area (odds ratio, 1.36;  $P=0.006$ ). Ex-PHT was associated with reduced cardiac event-free survival (at 3 years,  $22\pm 7\%$  versus  $55\pm 9\%$ ;  $P=0.014$ ). In a multivariable Cox proportional hazards model, Ex-PHT was identified as an independent predictor of cardiac events (hazard ratio, 1.8; 95% confidence interval, 1.0–3.3;  $P=0.047$ ). When exercise-induced changes in mean aortic pressure gradient were added to the multivariable model, Ex-PHT remained independently associated with reduced cardiac event-free survival (hazard ratio, 2.0; 95% confidence interval, 1.1–3.6;  $P=0.025$ ).

**Conclusions**—In asymptomatic patients with severe aortic stenosis, the main determinants of Ex-PHT are male sex, resting systolic pulmonary arterial pressure, and exercise parameters of diastolic burden. Moreover, Ex-PHT is associated with a 2-fold increased risk of cardiac events. These results strongly support the use of exercise stress echocardiography in asymptomatic aortic stenosis. (*Circulation*. 2012;126:851–859.)

**Key Words:** aortic valve stenosis ■ exercise ■ echocardiography ■ heart valves ■ hypertension, pulmonary

The management and the timing of surgery in asymptomatic patients with severe aortic stenosis (AS) remain matters of concern. In this setting, valve replacement is recommended when the left ventricular (LV) ejection fraction (LVEF) is reduced ( $<50\%$ ). However, LVEF is often preserved in severe AS as a result of adapted LV remodeling to the increased afterload, often leading to late surgical referral. Furthermore, recent studies have shown that irreversible LV myocardial fibrosis may be present even when LVEF is preserved.<sup>1,2</sup>

### Editorial see p 803 Clinical Perspective on p 859

A recent registry reported that compared with the conventional treatment strategy (ie, wait for symptoms), early surgery in

patients with very severe AS was associated with an improved long-term survival by decreasing cardiac mortality.<sup>3</sup> However, surgeons may be reluctant to operate on asymptomatic patients. The risks of aortic valve surgery and late complications of prosthesis need to be balanced against the possible prevention of sudden death and lowering of cardiac mortality. Hence, early elective surgery could be proposed to selected patients with a high risk of rapid LV function deterioration or symptomatic status impairment (ie, high risk of poor outcome).<sup>4,5</sup> This strategy requires the identification of accurate markers of poor outcome. In this regard, the presence of pulmonary hypertension (PHT) in patients with severe AS seems to be associated with a poorer prognosis<sup>6,7</sup> and a higher mortality rate after valve replacement<sup>8</sup> and represents an independent predictor of hospital

Received December 20, 2011; accepted June 14, 2012.

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*Circulation* is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.111.088427

mortality and postoperative major adverse cardiovascular and cerebrovascular events.<sup>9</sup> In patients receiving transcatheter aortic valve implantation, PHT was a strong independent predictor of poor outcome, augmenting by 2 the risk of late mortality.<sup>10</sup>

We have recently identified that exercise PHT in asymptomatic patients with primary mitral regurgitation was a good marker of a high risk of reduced symptom-free survival. To the best of our knowledge, the prognostic value of exercise PHT in AS is still unknown. The aim of this study was to identify the determinants and the potential prognostic importance of exercise PHT in asymptomatic patients with severe AS.

## Methods

We prospectively included consecutive patients with asymptomatic severe AS ( $n=195$ ), defined as an aortic valve area indexed for body size area  $<0.6 \text{ cm}^2/\text{m}^2$ , and preserved LVEF ( $\geq 55\%$ ) who were referred to our laboratory for exercise stress echocardiography. Only patients with a normal exercise stress test (ie, truly asymptomatic patients) were considered for the final analysis of the study, resulting in the exclusion of 45 patients with abnormal exercise response. The other exclusion criteria were (1) more than mild concomitant valvular heart disease ( $n=3$ ), (2) atrial fibrillation ( $n=2$ ), (3) known pulmonary disease ( $n=1$ ), (4) inability to perform an exercise test ( $n=4$ ), and (5) the absence of measurable systolic pulmonary arterial pressure (SPAP) at exercise ( $n=35$ ). The final population was composed of 105 patients (age,  $71 \pm 9$  years; male, 59%). The baseline demographic and clinical data were standardized and collected at the time of exercise stress echocardiography.

## Echocardiographic Study

Before the exercise stress test, resting comprehensive transthoracic echocardiography was performed with the VIVID 7 ultrasound system (General Electric Healthcare, Little Chalfont, UK). All Doppler echocardiographic recordings were stored on a dedicated workstation for subsequent offline analysis. For each measurement, at least 2 cardiac cycles were averaged. Continuous-wave Doppler was used to measure the aortic transvalvular maximal velocities; peak and mean gradients were calculated with the simplified Bernoulli equation ( $\Delta P=4v^2$ , where  $v$  is maximal aortic velocity in meters per second). LV stroke volume was calculated by multiplying the LV outflow tract area by the LV outflow tract velocity–time integral measured by pulsed-wave Doppler. Aortic valve area was calculated with the continuity equation. The biapical Simpson disk method was applied to quantify LV end-diastolic and end-systolic volumes and EF. In addition to this conventional evaluation of LV systolic function, 2-dimensional speckle tracking analysis (2-dimensional strain) was performed to quantify global longitudinal myocardial deformation as previously described.<sup>5,11</sup> Briefly, 2-dimensional strain is a non-Doppler-based method using standard 2-dimensional images with a frame rate acquisition  $>60 \text{ Hz}$ . By tracing the endocardial borders on an end-systolic frame, the software automatically tracked the contour on the subsequent frames. Adequate tracking was verified in real-time and was manually corrected when necessary. The global longitudinal deformation strain represents the average of the segment strains from the conventional apical 4-, 3-, and 2-chamber views. Left atrial (LA) area was obtained by planimetry of an end-systolic frame from the apical 4-chamber view. Peak E- and A-wave velocities of the mitral inflow were measured with pulsed-wave Doppler. Tissue Doppler imaging was applied for the measurement of the  $e'$  wave. The average of septal and lateral mitral annulus E $a$ -wave velocities was used to calculate the E/ $e'$  ratio.

SPAP was derived from the regurgitant jet of tricuspid regurgitation using systolic transtricuspid pressure gradient and adding 10 mm Hg for right atrial pressure as previously performed.<sup>12,13</sup> Resting PHT and exercise PHT were defined as SPAP  $>50$  and  $>60$  mm Hg, respectively. Right atrial pressure was assumed to be constant from rest to exercise.

## Exercise Protocol

A symptom-limited graded maximum bicycle exercise test was performed in the semisupine position on a tilt table. After an initial workload of 25 W maintained for 2 minutes, the workload was increased every 2 minutes by 25 W. A 12-lead ECG was monitored continuously, and blood pressure was measured at rest and every 2 minutes during exercise. If patients were on  $\beta$ -blockers, they were asked to stop their medication 24 hours before the test. The other medications, if any, were left unchanged. Patients with an abnormal exercise test were excluded from the present study. Abnormal exercise test was defined as (1) the occurrence of limiting breathlessness or fatigue at low workload ( $<75 \text{ W}$ ); (2) the occurrence of angina, dizziness, syncope, or near syncope; (3) a fall in systolic blood pressure below baseline or a rise in systolic blood during exercise  $<20 \text{ mm Hg}$ ; (4)  $\geq 2\text{-mm}$  ST-segment depression compared with baseline levels; and (5) complex ventricular arrhythmia.

## Event-Free Survival

Follow-up information was obtained every 6 to 12 months from standardized interviews with the patients, their physicians, or, if necessary, their next of kin according to guidelines.<sup>14,15</sup> The primary outcome variable was the time to occurrence of the first composite end point defined as cardiovascular death or need for aortic valve replacement motivated by the development of symptoms or LV systolic dysfunction. The patients' personal physicians determined the clinical management of the patients independently.

## Statistical Analysis

Results are expressed as mean  $\pm$  SD or percentage unless otherwise specified. Data comparisons were performed according to the presence or absence of exercise PHT using the Student unpaired  $t$  test,  $\chi^2$  test, or Fisher exact test as appropriate. The prevalence of PHT at rest and during exercise was compared by use of McNemar test. The significant changes from rest to exercise in continuous variables were assessed with a paired  $t$  test. The relationships between exercise SPAP and other continuous variables (ie, demographic data, exercise data, and resting and exercise echocardiographic data) were evaluated by simple linear regression. Independent predictors of exercise SPAP were obtained with the use of stepwise multiple linear regression. Predictors of exercise PHT were determined with stepwise logistic regression. In both multiple linear regression and logistic regression, variables with a univariable value of  $P<0.10$  were incorporated into the multiple regression; then, variables with a value of  $P>0.20$  were removed. Sensitivity, specificity, positive predictive value, and negative predictive value for the prediction of the occurrence of cardiac event were determined for various cutoff values of exercise SPAP with receiver-operating characteristic curves.

Probabilities of event-free survival were obtained by Kaplan-Meier estimates for the 2 groups and then compared by a 2-sided log-rank test.

The impact of exercise PHT on event-free survival was assessed with Cox proportional hazards models in univariable and multivariable analyses. Variables with a univariable value of  $P<0.10$  were incorporated into the multivariable models. The selection of variables included in the multivariate model was performed with special care. To avoid collinearity among a subset of several variables measuring the same phenomenon (eg, aortic valve area, peak gradient, mean gradient), we entered into the multivariate models the variable that had the strongest association with event-free survival on univariable analysis. In addition, to assess the accuracy of the prediction of a cardiac event by each model, we generated the Harrell correspondence index (C statistic).

Values of  $P<0.05$  were considered significant. All statistical analyses were performed with STATISTICA version 7 (StatSoft Inc, Tulsa, OK).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Table 1. Demographic, Clinical, and Exercise Data**

Variables	Whole Cohort (n=105)	No Exercise PHT (n=47, 45%)	Exercise PHT (n=58, 55%)	P
Demographic and clinical data				
Age, y	71±9	71±7	71±9	0.77
Male sex, n (%)	62 (59)	23 (49)	39 (67)	0.03
Body surface area, m <sup>2</sup>	1.8±0.2	1.8±0.2	1.8±0.2	0.81
Heart rate, bpm	71±13	73±14	68±12	0.04
Systolic arterial pressure, mm Hg	142±20	139±19	144±20	0.13
Diastolic arterial pressure, mm Hg	76±11	76±12	77±10	0.64
Risk factors, n (%)				
Hypertension	69 (66)	28 (60)	41 (71)	0.21
Overweight	36 (34)	15 (32)	21 (36)	0.68
Dyslipidemia	54 (51)	24 (51)	30 (52)	0.94
Diabetes mellitus	18 (17)	9 (19)	9 (16)	0.68
Smoker	35 (33)	14 (30)	21 (36)	0.63
LV hypertrophy	51 (49)	27 (57)	25 (43)	0.14
Exercise data				
Maximal exercise capacity, METs	4.8±1.2	4.6±0.8	4.9±1.3	0.12
Percentage of predicted exercise capacity, %	64±14	64±12	63±15	0.74
Heart rate, bpm	119±17	118±17	119±17	0.62
Systolic arterial pressure, mm Hg	177±22	174±20	179±23	0.20
Diastolic arterial pressure, mm Hg	86±14	85±15	87±13	0.52

PHT indicates pulmonary arterial hypertension; LV, left ventricular; and MET, metabolic equivalents.

## Results

### Population Characteristics

PHT, as previously defined, was significantly more frequent during exercise (55% versus 6%;  $P<0.0001$ ) than at rest. Patients with exercise PHT were more frequently male and had significant lower resting heart rate than those with no exercise PHT (Table 1). In addition, all patients with resting PHT ( $n=6$ ; Table 2) also developed exercise PHT ( $P=0.027$ , resting PHT prevalence in exercise PHT versus the no exercise PHT group). There was no other significant difference between the 2 groups in terms of demographic, clinical, or exercise data, as well as risk factors and medications. The maximal exercise capacity reached was  $4.8\pm1.2$  metabolic equivalents (METs;  $64\pm14\%$  of the predicted METs), ranging from 2.3 to 8.6 METs with no significant difference between the 2 groups ( $P=0.12$  and  $P=0.74$  for the percentage of predicted METs).

### Resting and Exercise Echocardiography

SPAP significantly increased from rest to exercise (from  $38\pm8$  to  $62\pm16$  mm Hg;  $P<0.0001$ ). Patients with exercise PHT had significant higher resting SPAP ( $P<0.0001$ ; Table 2) and exercise-induced changes in SPAP ( $14.9\pm7$  versus  $33.6\pm10$  mm Hg;  $P<0.0001$ ; Figure 1A and 1B). In patients with exercise PHT, the mean relative change in SPAP was  $121\pm61\%$ . During exercise, SPAP was doubled in 10 patients (21%) without exercise PHT and in 32 patients (56%;  $P<0.0001$ ) with exercise PHT.

Compared with patients with no exercise PHT, those with exercise PHT (Table 2) had higher resting and exercise indexed LV end-diastolic volume ( $P=0.045$  and  $P=0.04$ )

and more severe resting and exercise AS (peak transaortic gradient,  $P=0.046$  and  $P=0.008$ ; mean transaortic gradient,  $P=0.04$  and  $P=0.04$ ), higher exercise e'-wave velocity ( $P=0.004$ ), and larger exercise indexed LA area ( $P=0.001$ ). There were also trends for significantly higher resting and exercise E-wave velocity ( $P=0.10$  and  $P=0.07$ ) and exercise indexed LV end-systolic volume ( $P=0.07$ ).

### Determinants of Exercise SPAP and PHT

In simple linear regression, exercise SPAP was significantly correlated with resting SPAP ( $r=0.57$ ,  $P<0.0001$ ), heart rate ( $r=-0.20$ ,  $P=0.045$ ), E-wave velocity ( $r=0.19$ ,  $P=0.05$ ), exercise e'-wave velocity ( $r=0.19$ ,  $P=0.009$ ), and indexed LV end-diastolic volume ( $r=0.17$ ,  $P=0.044$ ). Both resting and exercise peak ( $r=0.23$ ,  $P=0.02$ ; and  $r=0.29$ ,  $P=0.003$ ) and mean ( $r=0.23$ ,  $P=0.016$ ; and  $r=0.24$ ,  $P=0.013$ ) transaortic pressure gradients were significantly correlated with exercise SPAP. In addition, the best correlation was found between exercise SPAP and exercise-induced changes in indexed LA area ( $r=0.40$ ,  $P<0.0001$ ). Multiple linear regression revealed that the independent predictors of exercise SPAP were exercise e'-wave velocity ( $\beta=11\pm5$ ;  $P=0.046$ ), exercise indexed LV end-diastolic volume ( $\beta=0.14\pm0.07$ ;  $P=0.038$ ), resting SPAP ( $\beta=0.9\pm0.2$ ;  $P<0.0001$ ), and exercise-induced changes in indexed LA area ( $\beta=1.3\pm0.4$ ;  $P=0.001$ ).

On multivariable analysis, with logistic regression (Table 3), the independent predictors of exercise PHT were male sex (odds ratio, 4.3;  $P=0.002$ ), resting SPAP (odds ratio, 1.16;  $P=0.002$ ), exercise indexed LV end-diastolic volume (odds ratio, 1.04;  $P=0.026$ ), exercise e'-wave velocity (odds ratio,



**Table 2. Resting and Exercise Echocardiographic Data**

Variables	Whole Cohort (n=105)	No Exercise PHT (n=47, 45%)	Exercise PHT (n=58, 55%)	P
<b>Resting LV function</b>				
Indexed LV end-systolic volume, mL/m <sup>2</sup>	19±10	19±9	20±11	0.64
Indexed LV end-diastolic volume, mL/m <sup>2</sup>	54±17	51±15	57±18	0.045
LV ejection fraction, %	67±7.6	66±7.5	67.5±7.7	0.40
LV global longitudinal strain, %	−16.3±2.6	−16.3±2.5	−16.2±2.7	0.82
E-wave velocity, cm/s	0.80±0.2	0.76±0.2	0.84±0.2	0.10
A-wave velocity, cm/s	0.93±0.3	0.89±0.3	0.97±0.3	0.23
e′-wave velocity, cm/s	7.8±2.2	7.6±1.8	8.0±2.5	0.35
E/A ratio	0.92±0.4	0.90±0.3	0.94±0.4	0.64
E/e′ ratio	10.9±3.6	10.4±3.1	11.2±4.1	0.28
<b>Exercise LV function</b>				
Indexed LV end-systolic volume, mL/m <sup>2</sup>	18±8.3	17±7.3	20±8.9	0.07
Indexed LV end-diastolic volume, mL/m <sup>2</sup>	54±17	50±15	57±19	0.04
LV ejection fraction, %	67±9	67±8	66±10	0.41
E-wave velocity, cm/s	1.27±0.3	1.22±0.3	1.33±0.3	0.07
A-wave velocity, cm/s	1.01±0.3	0.98±0.3	1.05±0.3	0.43
e′-wave velocity, cm/s	10.1±2.7	9.2±2.1	10.8±3.0	0.004
E/A ratio	1.35±0.6	1.25±0.4	1.44±0.8	0.25
E/e′ ratio	13.4±5.2	13.3±4.6	13.4±6.0	0.94
<b>Resting aortic stenosis severity</b>				
Peak transaortic gradient, mm Hg	72±23	67±19	76±26	0.046
Mean transaortic gradient, mm Hg	45±15	42±12	47±16	0.04
Aortic valve area, cm <sup>2</sup>	0.89±0.1	0.88±0.1	0.90±0.1	0.59
Indexed aortic valve area, cm/m <sup>2</sup>	0.50±0.1	0.49±0.1	0.50±0.1	0.63
<b>Exercise aortic stenosis severity</b>				
Peak transaortic gradient, mm Hg	91±28	83±21	97±31	0.008
Mean transaortic gradient, mm Hg	57±18	53±14	60±20	0.04
Aortic valve area, cm <sup>2</sup>	0.97±0.3	0.95±0.2	0.99±0.3	0.41
Indexed aortic valve area, cm/m <sup>2</sup>	0.54±0.16	0.53±0.1	0.55±0.2	0.46
Resting indexed LA area, cm <sup>2</sup> /m <sup>2</sup>	12.5±3.4	12.7±4	12.3±3	0.64
Exercise indexed LA area, cm <sup>2</sup> /m <sup>2</sup>	11.2±3.6	9.8±3.6	12.2±3.4	0.001
Resting PHT, n (%)	6 (6)	0 (0)	6 (10)	0.027
Resting SPAP, mm Hg	38±8	34±6	41±8	<0.0001
Exercise SPAP, mm Hg	62±16	48±9	74±9	<0.0001

PHT indicates pulmonary arterial hypertension; LV indicates left ventricular; LA, left atrial; and SPAP, systolic pulmonary arterial pressure.

1.35;  $P=0.047$ ), and exercise-induced changes in indexed LA area (odds ratio, 1.36;  $P=0.006$ ).

### Cardiac Event-Free Survival

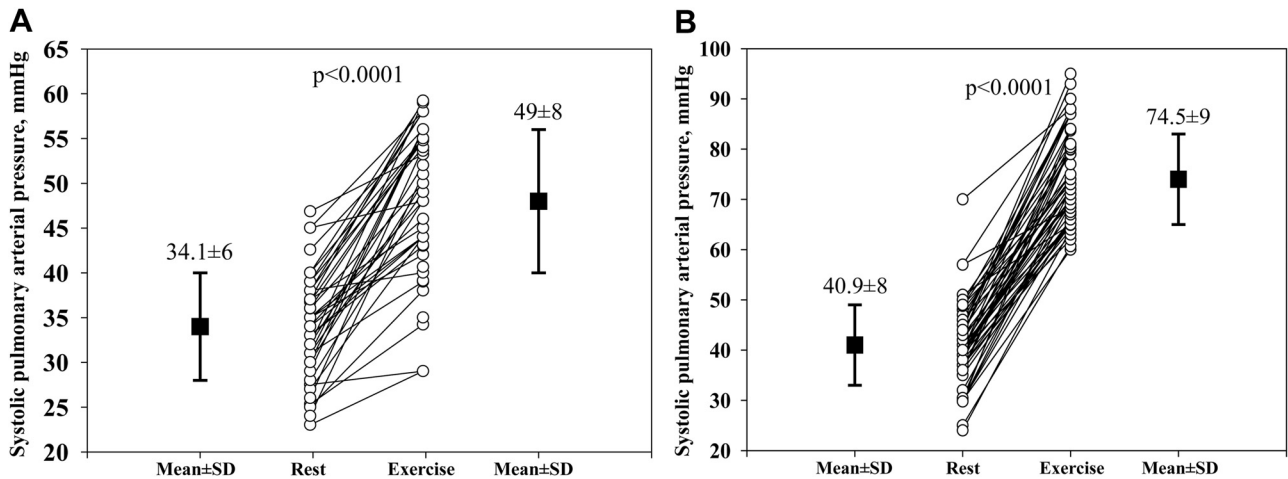
The follow-up was complete in all patients (100%). The mean follow-up time was 19±11 months (median, 16 months; range, 2–48 months). During follow-up, 56 patients (53%) fulfilled the predefined end point, resulting in event-free survival of 72±4%, 50±5%, and 34±6% at the 1-, 2-, and 3-year follow-up, respectively. There were 7 cardiovascular deaths during the follow-up (3 sudden deaths and 4 deaths after heart failure hospitalization). Of note, the 7 patients who died had developed exercise PHT (12%), but only 1 had resting PHT ( $P=0.014$ ). The remaining cardiac events were

aortic valve replacement dictated by the onset of symptoms ( $n=49$ ). The main indication for surgery was the occurrence of syncope ( $n=4$ ), angina ( $n=6$ ), dyspnea ( $n=38$ ), and significant arrhythmia ( $n=1$ ).

During the follow-up, among the 6 patients with resting PHT, 1 died, 2 underwent an aortic valve replacement, and 3 remained free of event.

The raw rate of cardiac event (number of patients with an event divided by total number of patients in each group) was significantly higher in patients with exercise PHT ( $n=39$  versus  $n=17$ , 67% versus 36%;  $P=0.0015$ ).

Patients with exercise PHT had lower cardiac event-free survival (at 1 year, 65±6% versus 81±6%; at 2 years, 43±7% versus 59±8%; at 3 years, 22±7% versus 55±9%;  $P=0.014$ ;



**Figure 1.** Impact of exercise on systolic pulmonary arterial pressure in patients without exercise pulmonary hypertension (A) and with exercise pulmonary hypertension (B).

Figure 2). In univariable analysis, exercise PHT was associated with 2-fold increase in cardiac events compared with patients without exercise PHT ( $P=0.017$ ; Table 4). Other univariable predictors of cardiac event were peak aortic jet velocity (hazard ratio [HR], 2; 95% confidence interval [CI], 1.35–2.97;  $P=0.001$ ), mean aortic transvalvular gradient (HR, 1.03; 95% CI, 1.01–1.04;  $P=0.02$ ), LV filling time (HR, 1.01; 95% CI, 1.00–1.01;  $P=0.014$ ), indexed LV end-systolic volume (HR, 1.03; 95% CI, 1.01–1.05;  $P=0.018$ ), indexed LV end-diastolic volume (HR, 1.02; 95% CI, 1.01–1.04;  $P=0.002$ ), and indexed LA area (HR, 1.06; 95% CI, 1.00–1.13;  $P=0.049$ ). Of note, exercise capacity, as assessed by the maximal reached METs, was not associated with reduced cardiac-event free survival (HR, 1.83; 95% CI, 0.7–4.8;  $P=0.21$ ), and none of the other exercise parameters was associated with outcome.

Resting PHT ( $n=6$ ) was not associated with reduced cardiac event-free survival ( $P=0.37$ ). However, there was a significant relationship between resting SPAP and outcome (HR, 1.03; 95% CI, 1.00–1.06;  $P=0.03$ ). This relationship remained significant after adjustment for age and sex (HR, 1.04; 95% CI, 1.00–1.07;  $P=0.03$ ) but not after adjustment for peak or mean aortic transvalvular gradient (HR, 1.03; 95% CI, 0.99–1.06;  $P=0.135$ ; and HR, 1.03; 95% CI, 0.99–1.06;  $P=0.08$ , respectively). Further adjustment with other resting echocardiographic data led

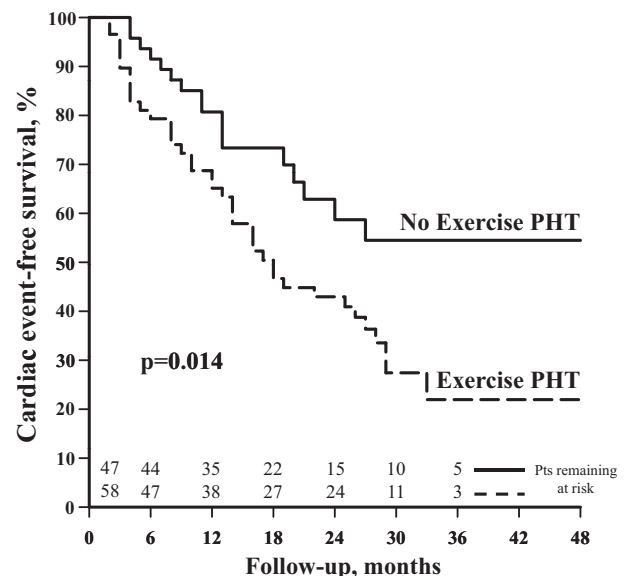
to a definite nonsignificant association between resting SPAP and cardiac event-free survival (HR, 1.03; 95% CI, 0.99–1.07;  $P=0.15$ ).

After adjustment for age and sex, exercise PHT was independently associated with reduced cardiac event-free survival (HR, 1.9; 95% CI, 1.1–3.4;  $P=0.025$ ; Table 4). With further adjustment including resting echocardiographic data, exercise PHT remained independently associated with cardiac events (HR, 1.8; 95% CI, 1.0–3.3;  $P=0.047$ ). As previously reported, exercise-induced changes in mean transaortic pressure gradient were associated with reduced event-free survival (HR, 1.02; 95% CI, 1.01–1.03;  $P=0.003$ ). In the multivariable model (Table 4), after adjustment for age, sex, resting echocardiographic data, and exercise-induced changes in mean transvalvular pressure gradient, exercise PHT remained an independent predictor of high risk of cardiac events (HR, 2.0; 95% CI, 1.1–3.6;  $P=0.025$ ). Of note, in this multivariable model, exercise-induced change in mean transaortic pressure gradient was also an independent predictor of events ( $P=0.043$ ).

**Table 3. Logistic Regression: Independent Determinants of Exercise Pulmonary Arterial Hypertension**

Variables	Odds Ratio	95% CI	P
Male sex	4.3	1.2–15.1	0.002
Resting SPAP (per mm Hg)	1.16	1.06–1.27	0.002
Exercise indexed LV end-diastolic volume (per mL/m <sup>2</sup> )	1.04	1.00–1.07	0.026
Exercise-induced changes in indexed LA area (per cm <sup>2</sup> /m <sup>2</sup> )	1.36	1.1–1.7	0.006
Exercise e'-wave velocity (per cm/s)	1.35	1.00–1.8	0.047

CI indicates confidence interval; SPAP, systolic pulmonary arterial pressure; LV, left ventricular; and LA, left atrial. Adjustment performed with age, resting heart rate, resting mean transaortic pressure gradient, exercise peak transaortic pressure gradient, exercise e'-wave velocity, and exercise indexed LV end-systolic volume.



**Figure 2.** Cardiac event-free survival according to the presence or absence of exercise pulmonary hypertension (PHT).

**Table 4. Cox Proportional Hazards Regression Analysis for the Prediction of Cardiac Event-Free Survival**

Models	Exercise PHT		
	Hazard Ratio	95% CI	P
Univariable	2.0	1.1–3.5	0.017
Age and sex adjusted	1.9	1.1–3.4	0.025
Resting data adjusted*	1.8	1.1–3.3	0.045
Exercise data adjusted†	2.0	1.1–3.6	0.025

PHT indicates pulmonary arterial hypertension; CI, confidence interval.

\*Adjustment including age, sex, indexed left atrial area, left ventricular end-systolic volume, left ventricular end-diastolic volume, E/e' ratio, and peak aortic jet velocity.

†Adjustment including age, sex, resting echocardiographic data, and exercise-induced changes in mean transaortic pressure gradient.

Using receiver-operating characteristic curve analysis, we found that exercise SPAP had a good accuracy for predicting cardiac events (area under the curve, 0.69). Of interest, the best cutoff value to predict cardiac events was exercise SPAP >60 mm Hg: sensitivity, 70%; specificity, 62%; positive predictive value, 67%; and negative predictive value, 64%.

In addition, to assess whether exercise SPAP was more accurate than resting SPAP in predicting cardiac events, we generated the C statistic for each model. The C statistics were systematically higher with exercise SPAP than resting SPAP in univariate age- and sex-adjusted or age-, sex-, and resting echocardiographic data-adjusted models (0.610 versus 0.515, 0.613 versus 0.557, and 0.664 versus 0.611, respectively).

### Incremental Prognostic Value of Exercise PHT Over Resting AS Severity

In the whole multivariate model, peak aortic jet velocity was the strongest resting echocardiographic predictor of outcome (HR, 1.02; 95% CI, 1.01–1.03;  $P<0.0001$ ). Figure 3 shows the incremental value of exercise PHT over markedly elevated peak aortic jet velocity (>4.0 m/s) in the prediction of cardiac events. The combination of high peak aortic jet velocity and exercise PHT resulted in the worse outcome ( $P=0.008$ ). Compared with the whole cohort, patients with high peak aortic jet

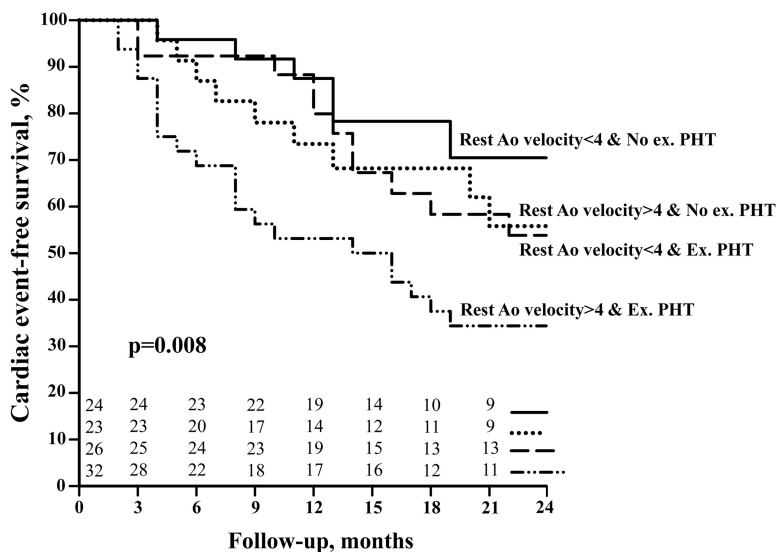
velocity and exercise PHT had a 2.4-fold increased risk of reduced event-free survival (95% CI, 1.4–4.03;  $P=0.002$ ). Reducing the analysis only to the subset of patients with markedly elevated peak aortic jet velocity resulted in a significant impact of exercise PHT on outcome (HR, 2.4; 95% CI, 1.1–5.2;  $P=0.014$ ). Of note, patients with exercise PHT but without markedly elevated peak aortic jet velocity had a 2-year event-free survival ( $54\pm 10\%$  versus  $56\pm 11\%$ ;  $P=0.77$ ) similar to that of patients with markedly elevated peak aortic jet velocity but without exercise PHT. Furthermore, the 7 deaths occurring during the follow-up were in patients with both markedly elevated peak aortic jet velocity and exercise PHT ( $P=0.001$ ).

### Discussion

The main findings of the present study are that (1) exercise PHT (ie, exercise SPAP >60 mm Hg) is a frequent condition (55% of the cohort) in patients with asymptomatic severe AS and preserved LVEF; (2) the independent determinants of exercise PHT are male sex, resting SPAP, and exercise parameters of diastolic burden (exercise indexed LV end-diastolic volume, exercise e'-wave velocity, and exercise-induced changes in indexed LA area); (3) exercise PHT is associated with an alarming rate of cardiac death (12%) and with significant reduced cardiac event-free survival; (4) exercise PHT doubles the risk of cardiac events independently of age, sex, resting echocardiographic data, and exercise-induced changes in mean transaortic pressure gradient; and (5) exercise PHT had an incremental prognostic value compared with resting AS severity parameter. Conversely, although resting elevated SPAP may affect clinical outcome, its prognostic value was weak in our study.

### Pulmonary Arterial Hypertension in AS

The prevalence of PHT varies considerably over studies according to patient selection criteria and the threshold used to define PHT. Overall, an SPAP >50 mm Hg is found in 15% to 30% of patients with severe AS,<sup>16–18</sup> and recently, severe SPAP (>60 mm Hg) was reported in 19% of a large cohort of 626 AS patients.<sup>19</sup>



**Figure 3.** Cardiac event-free survival according to the presence or absence of exercise pulmonary hypertension (Ex. PHT) and markedly elevated peak aortic (Ao) jet velocity (>4 m/s).



However, to the best of our knowledge, no study has reported the prevalence of PHT in truly asymptomatic patients. In our cohort, an SPAP >50 mm Hg was rare and identified in only 6 patients (6%), suggesting that the impact of severe AS on LV diastolic function<sup>20</sup> and LA geometry and function<sup>21,22</sup> may be generally well counterbalanced by LA compliance and/or pulmonary vascular resistance. Of interest, these patients with resting PHT were particularly old and had very severe AS, and half of them experienced cardiac events (including 1 death and 2 aortic valve replacement), suggesting the poor outcome of this subset. In contrast, a recent study has shown that PHT is frequent in surgery-referred patients with LV dysfunction and is independently associated with LA function impairment.<sup>23</sup>

The potential impact on outcome of PHT in patients with AS is also a source of debate. In 1979, McHenry et al<sup>7</sup> showed that PHT could be considered a harbinger for sudden death and clinical deterioration. More recently, PHT in severe AS was also associated with a dismal prognosis under conservative management.<sup>24,25</sup> Nevertheless, PHT may frequently and rapidly be abolished after aortic valve replacement,<sup>24–26</sup> leading to a more favorable long-term outcome.<sup>27</sup>

### Exercise PHT in AS

Exercise PHT was significantly more frequent (55%) than resting PHT (6%) in our cohort. This entity is characterized by lower resting heart rate and higher resting and peak exercise indexed LV end-diastolic volume. During exercise, whereas some patients with no exercise PHT may have only a mild increase in SPAP (Figure 1A), the vast majority of those with exercise PHT (Figure 1B) experienced a marked rise in SPAP. This phenomenon is essentially determined by the level of exercise  $e'$ -wave velocity, the exercise indexed LV end-diastolic volume, and the exercise-induced changes in indexed LA area.

In AS, the chronically increased afterload results in progressive LV remodeling and myocardial hypertrophy. Although the increase in LV wall thickness is a compensatory mechanism that reduces systolic wall stress, it can result in impaired LV relaxation, reduced LV compliance, and increased metabolic demands. The ability of the LV to adequately fill under normal pressures is thus altered and the LV diastolic pressure increases. As a result, LA slowly expands and becomes dysfunctional and less compliant, making it impossible to limit the transmission to the pulmonary vascular bed of any further increase, even minimal, in LV end-diastolic pressure observed during exercise. Furthermore, any degree of LV diastolic dysfunction (relaxation abnormality) and increased LV filling pressure at rest and/or at exercise can be sufficient to trigger exercise PHT. In these patients, exercise echocardiography enables us to unmask a more advanced impairment in LV diastolic properties, namely latent LV diastolic dysfunction. This is line with our observations because exercise PHT was related mainly to exercise parameters of diastolic burden. Of note, a limitation in LA compliance was confirmed by the significant correlation observed between exercise-induced changes in indexed LA area and exercise SPAP. For a given increase in LV filling pressure, patients with limited changes in LA dimensions (ie, exhausted LA compliance reserve) during exercise displayed a higher

increase in SPAP; this is even truer if LA emptying is not facilitated any more from recruitable LA function.

### Clinical Implications

Our results are the first to demonstrate that the measurement of SPAP during exercise echocardiography may improve risk stratification of asymptomatic severe AS. Indeed, patients who experienced exercise PHT (SPAP >60 mm Hg) multiplied by 2 the risk of cardiac events, even after adjustment for demographic and resting and exercise echocardiographic data. Among the 7 cardiovascular-related deaths that occurred during follow-up, only 1 patient had resting PHT, but all of those patients had developed exercise PHT. Of interest, our data show that resting elevated SPAP is not independently associated with reduced cardiac event-free survival in “truly” asymptomatic patients with severe AS.

Hence, these results strongly emphasize the usefulness of exercise stress echocardiography in this clinical situation. Exercise PHT also had incremental prognostic value compared with AS severity parameters (ie, aortic jet velocity). Indeed, in patients with markedly elevated aortic jet velocity, those with exercise PHT exhibited a significant lower cardiac event-free survival (Figure 3) compared with the others, resulting in poorer outcome. Furthermore, patients with exercise PHT but without markedly elevated aortic jet velocity had a prognosis similar to that for those without exercise PHT but with high aortic jet velocity. Thus, in patients with asymptomatic AS and <4-m/s aortic jet velocity, the presence of exercise PHT is still able to identify a subset of patients at dismal prognosis (Figure 3) who may require a closer follow-up to look for any changes in LV diastolic function and symptoms.

During tests, an exercise-induced increase in mean transaortic pressure gradient by >18 to 20 mm Hg has recently been identified as a marker of poor prognosis in asymptomatic AS.<sup>28,29</sup> Our results confirm that this parameter is associated with reduced cardiac event-free survival, but we further show that exercise PHT is an predictor of impaired prognosis independently of the changes in LV afterload. Interestingly, only one third of patients with exercise PHT also had a marked increase in mean transaortic pressure gradient. This suggests that the presence of elevated exercise SPAP may unmask a subset of asymptomatic patients with latent LV diastolic dysfunction, reduced atrioventricular compliance, and impaired pulmonary vascular resistance. These patients are probably more subject to rapidly developing symptoms and seem to be at higher risk of cardiac-related death. Consequently, the use of exercise stress echocardiography in asymptomatic patients with severe AS could be recommended. At peak exercise, the measurement of both mean transaortic pressure gradient and SPAP, which are technically easy and rapid and have good reproducibility,<sup>13,29–32</sup> may improve the management of such patients. Indeed, the high rate of cardiac-related death observed in patients with exercise PHT (12%), despite normal exercise tests, should encourage prompt surgery, which is, in asymptomatic patients, associated with very low operative mortality<sup>3</sup> and low prosthesis-related complication rate. Conversely, patients with no exercise PHT and no marked increase in mean transaortic gradient can be followed up safely.

## Limitations

Apparent nonsignificant results may be related to the relatively small sample size of the study. Specifically, the absence of relationship between maximal exercise capacity parameters and cardiac event-free survival could be due mainly to a type II error. Nevertheless, this limitation does not affect the validity of the main result of the study, which is the demonstration that exercise PHT may have an incremental prognostic value in patients with asymptomatic severe AS.

Despite careful assessment, the evaluation of the occurrence of symptoms at a low workload during exercise remains subjective. Hence, although rare, it is possible that some patients with symptoms during exertion were included in the final population.

As in our previous studies,<sup>13,33</sup> the right atrial pressure was estimated at 10 mm Hg both at rest and during exercise. Hence, we may have missed the potential influence of exercise-induced changes in right atrial pressure. Nevertheless, the noninvasive evaluation of right atrial pressure during exercise (ie, when venous compliance is known to decrease) with noninvasive methods such as Doppler echocardiography remains difficult, is probably subject to low accuracy, and is not validated. Moreover, right atrial pressure is frequently assumed to be 5 mm Hg in normal subjects<sup>30</sup> and 10 mm Hg in patients with valvular disease.<sup>12</sup>

The absence of evaluation of the presence and extent of coronary artery disease in patients not referred to surgery is also a limitation of this report. However, these patients have, by definition, no resting symptoms and normal LVEF and exercise test, suggesting that they are truly asymptomatic. In this context, coronary angiography is not recommended, and the rate of significant coronary artery disease in our population is probably low.

## Conclusions

In asymptomatic patients with severe AS, the main determinants of exercise PHT are male sex, resting SPAP, and exercise parameters of diastolic burden. Exercise PHT is associated with a 2-fold increased risk of cardiac events and provides incremental prognostic value independently of demographic, resting echocardiographic data, and exercise-induced changes in mean transaortic pressure gradient. These results support the use of exercise stress echocardiography in asymptomatic AS.

## Acknowledgments

We thank M. Carmine Celentano for excellent technical assistance.

## Sources of Funding

Dr Magne is research associate from the F.R.S-FNRS, Brussels, Belgium, and received grants from the Fonds Léon Fredericq, Liège, Belgium, and from the Fond pour la Chirurgie Cardiaque, Belgium.

## Disclosures

None.

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### CLINICAL PERSPECTIVE

The management and timing of surgery in asymptomatic patients with severe aortic stenosis remain matters of concern. The risks of aortic valve surgery and late complications of prosthesis in such patients need to be balanced against the possible prevention of sudden death and lowering of cardiac mortality. Hence, early elective surgery could be proposed only to well-selected patients considered at high risk of poor outcome. In the present study, 105 consecutive asymptomatic patients with severe aortic stenosis underwent comprehensive resting and exercise stress echocardiography to evaluate the presence of pulmonary hypertension (PHT). The results showed that 55% of asymptomatic patients may develop exercise PHT. Patients with exercise PHT had significantly lower cardiac event-free survival and a markedly higher rate of death than those without exercise PHT. In addition, exercise PHT was associated with poorer outcome independently of demographic and resting echocardiographic data and exercise-induced changes in mean transaortic pressure gradient. Beyond both resting aortic stenosis severity and systolic pulmonary arterial pressure, the assessment of the presence of exercise PHT provided important incremental predictive value. Even in patients with markedly elevated aortic jet velocity, those with exercise PHT depicted a higher risk of reduced cardiac event-free survival. These results strongly support the use of exercise stress echocardiography in the management of asymptomatic severe aortic stenosis. Early elective aortic valve surgery to prevent irreversible left ventricular myocardial damage, diastolic dysfunction, and symptoms could be advised in patients developing exercise PHT. In contrast, asymptomatic patients with no exercise PHT may be conservatively followed up.

# 운동시 폐고혈압은 무증상 대동맥판협착증의 새로운 위험신호이다

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## Summary

### 배경

최근 연구 결과에서 무증상의 대동맥판협착증 환자에서 운동 심초음파(exercise stress echocardiography) 검사의 유용성이 증명된 바 있다. 하지만 이들 환자에서 운동시 폐고혈압의 의미에 대해서는 알려진 바가 별로 없다. 본 연구의 저자들은 무증상의 중증 대동맥판협착증 환자에서 운동시 폐고혈압의 결정인자와 예후에 대한 영향을 알아보려고 하였다.

### 방법 및 결과

증상이 없으면서 좌심실 수축기능이 정상인(구혈률  $\geq 55\%$ ) 중증 대동맥판협착증 환자(총 105명, 대동맥판 면적  $< 0.6 \text{ cm}^2/\text{m}^2$ ; 평균 연령  $71 \pm 9$ 세; 남성 59%)를 전향적으로 모집하여 운동 심초음파 검사를 시행하였다. 안정시 및 운동시 폐고혈압은 각각 폐동맥 수축기압  $> 50 \text{ mmHg}$ 와  $> 60 \text{ mmHg}$ 를 기준으로 하였다. 운동시 폐고혈압은 안정시보다 흔하게 관찰되었다( $55\%$  vs.  $6\%$ ;  $P < 0.0001$ ). 다변량 로지스틱 회귀분석에서 운동시 폐고혈압의 독립적인 예측인자는 남성( $\text{OR } 4.3$ ;  $P = 0.002$ ), 안정시 폐동맥 수축기압( $\text{OR } 1.16$ ;  $P = 0.002$ ), 운동시 좌심실 이완기말 용적( $\text{OR } 1.04$ ;  $P = 0.026$ ), 운동

시 e'-파 속도( $\text{OR } 1.35$ ;  $P = 0.047$ ), 그리고 운동시 좌심방 면적의 변화였다( $\text{OR } 1.36$ ;  $P = 0.006$ ). 운동시 폐고혈압은 심혈관계 사건-free survival 감소와 관련 있었다(3년 후,  $22 \pm 7\%$  vs.  $55 \pm 9\%$ ;  $P = 0.014$ ). 또한, 다변량분석에서 운동시 폐고혈압은 심혈관계 사건의 독립적인 예측인자였다( $\text{HR } 1.8$ ;  $95\% \text{ CI } 1.0-3.3$ ;  $P = 0.047$ ). 운동시 대동맥판 압력차 상승을 다변량분석에 포함시키면, 운동시 폐고혈압은 심혈관계 사건-free survival 저하와 독립적으로 관련되었다( $\text{HR } 2.0$ ;  $95\% \text{ CI } 1.1-3.6$ ;  $P = 0.025$ ).

### 결론

무증상의 중증 대동맥판협착증 환자에서 운동시 폐고혈압의 주요 결정인자는 남성, 안정시 폐동맥 수축기압, 운동시 이완기 지표들이었다. 운동시 폐고혈압은 심혈관계 사건 발생 위험의 2배 증가와 관련있었다. 이런 결과들은 무증상의 대동맥판협착증 환자에서 운동 심초음파 검사의 유용성을 잘 보여준다.



## Commentary

중증 대동맥판협착증에 의한 좌심실의 압력 과부하는 좌심실비대와 섬유화를 유발하고, 관상동맥의 확장능을 감소시켜 좌심실의 수축 및 이완 기능장애를 초래하며, 궁극적으로는 호흡곤란, 흉통, 실신의 증상을 유발하고, 더 진행되면 사망에 이르게 된다. 증상이 발생하면 수술만이 증상과 좌심실 기능, 생존율을 개선시킬 수 있기 때문에 치료전략은 간단하다. 하지만 증상이 없는 환자에서 수술의 적응증에 대해서는 아직 논란이 많다. 현재까지의 가이드라인에서는 주의 깊은 관찰을 권고하고 있지만, 많은 연구를 통해 결국 3-5년 이내에 증상이 발생하거나 수술을 시행하게 되는 환자들이 적지 않다는 것이 잘 알려져 있으며, 일부 연구에서는 무증상 환자에서도 사망의 위험이 증가한다고 보고하고 있다. 대동맥판막 수술에 따른 위험도가 낮기 때문에, 최근 들어 무증상 환자 중 사망이나 증상 발생의 위험이 큰 군을 찾아 조기 수술을 시행하고자 하는 전문병원의 노력이 많은 주목을 받고 있다.

대동맥판협착증 환자에서 증상 유무를 제대로 평가하는 것은 때로는 쉽지 않다. 적지 않은 환자들이 증상에 맞게 활동량을 줄이기 때문에 증상이 없는 것으로 오인될 수 있으며, 또한, 고령, 운동 부족, 과체중 환자에서 흔히 보이는 경도의 호흡곤란을 심장질환에 의한 것으로 판단하는 데도 많은 어려움이 있다. 따라서 운동검사는 위험도가 높은 환자에서 증상 유무와 정상적인 혈압 반응을 평가하는 데 좋은 방법으로 제시되어 왔다. 즉, 운동검사에서 운동능력이 저하되어 있거나 혈압이 적절히 상승하지 않는 환자들이 수년 내에 증상이 발생하거나 수술을 받게 될 가능성이 높다는 것이다. 하지만 이런 연구들은 운동검사 결과 자체가 향후 치료방침을 결정하는 데 영향을 미칠 수 있으며, 증상의 원인이 심장인지 아닌지를 감별하는 데에도 주관적일 수밖에 없었다.

운동 심초음파검사는 도플러 에코를 통해 운동시 혈액역학적 변화를 평가할 수 있기 때문에 일반적인 운동검사에 비해 객관적인 수치를 제시할 수 있다는 장점이 있다. 과거 연구에서 운동시 대동맥판 압력차가 20mmHg 이상 증가하는 환자에서 향후에 증상이 발생하거나 사망할 가능성이 높았다.

본 연구에서 저자들은 기존에 알려진 운동시 대동맥판 압력차 외에 폐동맥 수축기압의 변화를 측정하여 운동시 폐고혈압이 발생하는 환자에서 수술, 심부전, 사망의 발생률이 높다는 것을 보고하였다. 특히, 운동능력이 저하되어 있거나(75W 미만), 운동 중 혈압이 20mmHg 이상 적절히 상승하지 않거나, ST분절이 2mm 이상 하강하는 이상반응을 보이는 환자들은 모두 제외했기 때문에 새로운 위험인자로서의 임상적 의미가 크다고 하겠다. 또한, 본 연구에서 폐동맥 수축기압의 상승은 좌심실의 이완기능이나 좌심방 크기와 연관되었는데, 이는 운동시 폐고혈압이 대동맥판협착증에 의한 좌심실의 변화를 잘 나타낸다고 하겠다.

하지만 본 연구의 결과가 곧 운동시 폐고혈압을 보이는 환자에서 조기수술이 필요하다는 의미는 아니다. 즉, 운동시 폐고혈압이 발생한 환자에서 위험도가 높았지만, 이 환자들에서 조기수술을 시행하는 것이 예후를 개선할 수 있다는 증거가 될 수는 없다. 따라서 향후 무증상의 중증 대동맥판협착증 환자에서 다양한 위험도 평가 방법을 개발하고, 그에 따른 조기수술이 예후에 미치는 영향에 대한 대규모 전향적 연구가 필요하겠다.

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# Determinants and Prognostic Significance of Exercise Pulmonary Hypertension in Asymptomatic Severe Aortic Stenosis

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**Background**—Recent studies emphasized the usefulness of exercise stress echocardiography in asymptomatic patients with aortic stenosis. Nevertheless, the additive value of exercise pulmonary hypertension (Ex-PHT) in such patients remains unexplored. We therefore aimed to identify the determinants and to test the impact on outcome of Ex-PHT in asymptomatic patients with severe aortic stenosis.

**Method and Results**—Asymptomatic patients with severe aortic stenosis ( $n=105$ ; aortic valve area  $<0.6$  cm<sup>2</sup>/m<sup>2</sup>; age,  $71\pm 9$  years; male, 59%) and preserved left ventricular systolic function (ejection fraction  $\geq 55\%$ ) were prospectively submitted to exercise stress echocardiography. Resting PHT and Ex-PHT were defined as a systolic pulmonary arterial pressure  $>50$  and  $>60$  mm Hg, respectively. Ex-PHT was more frequent than resting PHT (55% versus 6%;  $P<0.0001$ ). On multivariable logistic regression, the independent predictors of Ex-PHT were male sex (odds ratio, 4.3;  $P=0.002$ ), resting systolic pulmonary arterial pressure (odds ratio, 1.16;  $P=0.002$ ), exercise indexed left ventricular end-diastolic volume (odds ratio, 1.04;  $P=0.026$ ), exercise  $e'$ -wave velocity (odds ratio, 1.35;  $P=0.047$ ), and exercise-induced changes in indexed left atrial area (odds ratio, 1.36;  $P=0.006$ ). Ex-PHT was associated with reduced cardiac event-free survival (at 3 years,  $22\pm 7\%$  versus  $55\pm 9\%$ ;  $P=0.014$ ). In a multivariable Cox proportional hazards model, Ex-PHT was identified as an independent predictor of cardiac events (hazard ratio, 1.8; 95% confidence interval, 1.0–3.3;  $P=0.047$ ). When exercise-induced changes in mean aortic pressure gradient were added to the multivariable model, Ex-PHT remained independently associated with reduced cardiac event-free survival (hazard ratio, 2.0; 95% confidence interval, 1.1–3.6;  $P=0.025$ ).

**Conclusions**—In asymptomatic patients with severe aortic stenosis, the main determinants of Ex-PHT are male sex, resting systolic pulmonary arterial pressure, and exercise parameters of diastolic burden. Moreover, Ex-PHT is associated with a 2-fold increased risk of cardiac events. These results strongly support the use of exercise stress echocardiography in asymptomatic aortic stenosis. (*Circulation*. 2012;126:851-859.)

**Key Words:** aortic valve stenosis ■ exercise ■ echocardiography ■ heart valves ■ hypertension, pulmonary

The management and the timing of surgery in asymptomatic patients with severe aortic stenosis (AS) remain matters of concern. In this setting, valve replacement is recommended when the left ventricular (LV) ejection fraction (LVEF) is reduced ( $<50\%$ ). However, LVEF is often preserved in severe AS as a result of adapted LV remodeling to the increased afterload, often leading to late surgical referral. Furthermore, recent studies have shown that irreversible LV myocardial fibrosis may be present even when LVEF is preserved.<sup>1,2</sup>

## Clinical Perspective on p 126

A recent registry reported that compared with the conventional treatment strategy (ie, wait for symptoms), early surgery in

patients with very severe AS was associated with an improved long-term survival by decreasing cardiac mortality.<sup>3</sup> However, surgeons may be reluctant to operate on asymptomatic patients. The risks of aortic valve surgery and late complications of prosthesis need to be balanced against the possible prevention of sudden death and lowering of cardiac mortality. Hence, early elective surgery could be proposed to selected patients with a high risk of rapid LV function deterioration or symptomatic status impairment (ie, high risk of poor outcome).<sup>4,5</sup> This strategy requires the identification of accurate markers of poor outcome. In this regard, the presence of pulmonary hypertension (PHT) in patients with severe AS seems to be associated with a poorer prognosis<sup>6,7</sup> and a higher mortality rate after valve replacement<sup>8</sup> and represents an independent predictor of hospital

Received December 20, 2011; accepted June 14, 2012.

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*Circulation* is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.111.088427

mortality and postoperative major adverse cardiovascular and cerebrovascular events.<sup>9</sup> In patients receiving transcatheter aortic valve implantation, PHT was a strong independent predictor of poor outcome, augmenting by 2 the risk of late mortality.<sup>10</sup>

We have recently identified that exercise PHT in asymptomatic patients with primary mitral regurgitation was a good marker of a high risk of reduced symptom-free survival. To the best of our knowledge, the prognostic value of exercise PHT in AS is still unknown. The aim of this study was to identify the determinants and the potential prognostic importance of exercise PHT in asymptomatic patients with severe AS.

## Methods

We prospectively included consecutive patients with asymptomatic severe AS ( $n=195$ ), defined as an aortic valve area indexed for body size area  $<0.6 \text{ cm}^2/\text{m}^2$ , and preserved LVEF ( $\geq 55\%$ ) who were referred to our laboratory for exercise stress echocardiography. Only patients with a normal exercise stress test (ie, truly asymptomatic patients) were considered for the final analysis of the study, resulting in the exclusion of 45 patients with abnormal exercise response. The other exclusion criteria were (1) more than mild concomitant valvular heart disease ( $n=3$ ), (2) atrial fibrillation ( $n=2$ ), (3) known pulmonary disease ( $n=1$ ), (4) inability to perform an exercise test ( $n=4$ ), and (5) the absence of measurable systolic pulmonary arterial pressure (SPAP) at exercise ( $n=35$ ). The final population was composed of 105 patients (age,  $71 \pm 9$  years; male, 59%). The baseline demographic and clinical data were standardized and collected at the time of exercise stress echocardiography.

## Echocardiographic Study

Before the exercise stress test, resting comprehensive transthoracic echocardiography was performed with the VIVID 7 ultrasound system (General Electric Healthcare, Little Chalfont, UK). All Doppler echocardiographic recordings were stored on a dedicated workstation for subsequent offline analysis. For each measurement, at least 2 cardiac cycles were averaged. Continuous-wave Doppler was used to measure the aortic transvalvular maximal velocities; peak and mean gradients were calculated with the simplified Bernoulli equation ( $\Delta P=4v^2$ , where  $v$  is maximal aortic velocity in meters per second). LV stroke volume was calculated by multiplying the LV outflow tract area by the LV outflow tract velocity-time integral measured by pulsed-wave Doppler. Aortic valve area was calculated with the continuity equation. The biapical Simpson disk method was applied to quantify LV end-diastolic and end-systolic volumes and EF. In addition to this conventional evaluation of LV systolic function, 2-dimensional speckle tracking analysis (2-dimensional strain) was performed to quantify global longitudinal myocardial deformation as previously described.<sup>5,11</sup> Briefly, 2-dimensional strain is a non-Doppler-based method using standard 2-dimensional images with a frame rate acquisition  $>60 \text{ Hz}$ . By tracing the endocardial borders on an end-systolic frame, the software automatically tracked the contour on the subsequent frames. Adequate tracking was verified in real-time and was manually corrected when necessary. The global longitudinal deformation strain represents the average of the segment strains from the conventional apical 4-, 3-, and 2-chamber views. Left atrial (LA) area was obtained by planimetry of an end-systolic frame from the apical 4-chamber view. Peak E- and A-wave velocities of the mitral inflow were measured with pulsed-wave Doppler. Tissue Doppler imaging was applied for the measurement of the  $e'$  wave. The average of septal and lateral mitral annulus  $Ea$ -wave velocities was used to calculate the  $E/e'$  ratio.

SPAP was derived from the regurgitant jet of tricuspid regurgitation using systolic transtricuspid pressure gradient and adding 10 mm Hg for right atrial pressure as previously performed.<sup>12,13</sup> Resting PHT and exercise PHT were defined as  $\text{SPAP} >50$  and  $>60 \text{ mm Hg}$ , respectively. Right atrial pressure was assumed to be constant from rest to exercise.

## Exercise Protocol

A symptom-limited graded maximum bicycle exercise test was performed in the semisupine position on a tilt table. After an initial workload of 25 W maintained for 2 minutes, the workload was increased every 2 minutes by 25 W. A 12-lead ECG was monitored continuously, and blood pressure was measured at rest and every 2 minutes during exercise. If patients were on  $\beta$ -blockers, they were asked to stop their medication 24 hours before the test. The other medications, if any, were left unchanged. Patients with an abnormal exercise test were excluded from the present study. Abnormal exercise test was defined as (1) the occurrence of limiting breathlessness or fatigue at low workload ( $<75 \text{ W}$ ); (2) the occurrence of angina, dizziness, syncope, or near syncope; (3) a fall in systolic blood pressure below baseline or a rise in systolic blood during exercise  $<20 \text{ mm Hg}$ ; (4)  $\geq 2\text{-mm}$  ST-segment depression compared with baseline levels; and (5) complex ventricular arrhythmia.

## Event-Free Survival

Follow-up information was obtained every 6 to 12 months from standardized interviews with the patients, their physicians, or, if necessary, their next of kin according to guidelines.<sup>14,15</sup> The primary outcome variable was the time to occurrence of the first composite end point defined as cardiovascular death or need for aortic valve replacement motivated by the development of symptoms or LV systolic dysfunction. The patients' personal physicians determined the clinical management of the patients independently.

## Statistical Analysis

Results are expressed as mean  $\pm$  SD or percentage unless otherwise specified. Data comparisons were performed according to the presence or absence of exercise PHT using the Student unpaired  $t$  test,  $\chi^2$  test, or Fisher exact test as appropriate. The prevalence of PHT at rest and during exercise was compared by use of McNemar test. The significant changes from rest to exercise in continuous variables were assessed with a paired  $t$  test. The relationships between exercise SPAP and other continuous variables (ie, demographic data, exercise data, and resting and exercise echocardiographic data) were evaluated by simple linear regression. Independent predictors of exercise SPAP were obtained with the use of stepwise multiple linear regression. Predictors of exercise PHT were determined with stepwise logistic regression. In both multiple linear regression and logistic regression, variables with a univariable value of  $P < 0.10$  were incorporated into the multiple regression; then, variables with a value of  $P > 0.20$  were removed. Sensitivity, specificity, positive predictive value, and negative predictive value for the prediction of the occurrence of cardiac event were determined for various cutoff values of exercise SPAP with receiver-operating characteristic curves.

Probabilities of event-free survival were obtained by Kaplan-Meier estimates for the 2 groups and then compared by a 2-sided log-rank test.

The impact of exercise PHT on event-free survival was assessed with Cox proportional hazards models in univariable and multivariable analyses. Variables with a univariable value of  $P < 0.10$  were incorporated into the multivariable models. The selection of variables included in the multivariate model was performed with special care. To avoid collinearity among a subset of several variables measuring the same phenomenon (eg, aortic valve area, peak gradient, mean gradient), we entered into the multivariate models the variable that had the strongest association with event-free survival on univariable analysis. In addition, to assess the accuracy of the prediction of a cardiac event by each model, we generated the Harrell correspondence index (C statistic).

Values of  $P < 0.05$  were considered significant. All statistical analyses were performed with STATISTICA version 7 (StatSoft Inc, Tulsa, OK).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Table 1. Demographic, Clinical, and Exercise Data**

Variables	Whole Cohort (n=105)	No Exercise PHT (n=47, 45%)	Exercise PHT (n=58, 55%)	P
Demographic and clinical data				
Age, y	71±9	71±7	71±9	0.77
Male sex, n (%)	62 (59)	23 (49)	39 (67)	0.03
Body surface area, m <sup>2</sup>	1.8±0.2	1.8±0.2	1.8±0.2	0.81
Heart rate, bpm	71±13	73±14	68±12	0.04
Systolic arterial pressure, mm Hg	142±20	139±19	144±20	0.13
Diastolic arterial pressure, mm Hg	76±11	76±12	77±10	0.64
Risk factors, n (%)				
Hypertension	69 (66)	28 (60)	41 (71)	0.21
Overweight	36 (34)	15 (32)	21 (36)	0.68
Dyslipidemia	54 (51)	24 (51)	30 (52)	0.94
Diabetes mellitus	18 (17)	9 (19)	9 (16)	0.68
Smoker	35 (33)	14 (30)	21 (36)	0.63
LV hypertrophy	51 (49)	27 (57)	25 (43)	0.14
Exercise data				
Maximal exercise capacity, METS	4.8±1.2	4.6±0.8	4.9±1.3	0.12
Percentage of predicted exercise capacity, %	64±14	64±12	63±15	0.74
Heart rate, bpm	119±17	118±17	119±17	0.62
Systolic arterial pressure, mm Hg	177±22	174±20	179±23	0.20
Diastolic arterial pressure, mm Hg	86±14	85±15	87±13	0.52

PHT indicates pulmonary arterial hypertension; LV, left ventricular; and MET, metabolic equivalents.

## Results

### Population Characteristics

PHT, as previously defined, was significantly more frequent during exercise (55% versus 6%;  $P<0.0001$ ) than at rest. Patients with exercise PHT were more frequently male and had significant lower resting heart rate than those with no exercise PHT (Table 1). In addition, all patients with resting PHT ( $n=6$ ; Table 2) also developed exercise PHT ( $P=0.027$ , resting PHT prevalence in exercise PHT versus the no exercise PHT group). There was no other significant difference between the 2 groups in terms of demographic, clinical, or exercise data, as well as risk factors and medications. The maximal exercise capacity reached was  $4.8\pm1.2$  metabolic equivalents (METS;  $64\pm14\%$  of the predicted METs), ranging from 2.3 to 8.6 METs with no significant difference between the 2 groups ( $P=0.12$  and  $P=0.74$  for the percentage of predicted METs).

### Resting and Exercise Echocardiography

SPAP significantly increased from rest to exercise (from  $38\pm8$  to  $62\pm16$  mm Hg;  $P<0.0001$ ). Patients with exercise PHT had significant higher resting SPAP ( $P<0.0001$ ; Table 2) and exercise-induced changes in SPAP ( $14.9\pm7$  versus  $33.6\pm10$  mm Hg;  $P<0.0001$ ; Figure 1A and 1B). In patients with exercise PHT, the mean relative change in SPAP was  $121\pm61\%$ . During exercise, SPAP was doubled in 10 patients (21%) without exercise PHT and in 32 patients (56%;  $P<0.0001$ ) with exercise PHT.

Compared with patients with no exercise PHT, those with exercise PHT (Table 2) had higher resting and exercise indexed LV end-diastolic volume ( $P=0.045$  and  $P=0.04$ )

and more severe resting and exercise AS (peak transaortic gradient,  $P=0.046$  and  $P=0.008$ ; mean transaortic gradient,  $P=0.04$  and  $P=0.04$ ), higher exercise  $e'$ -wave velocity ( $P=0.004$ ), and larger exercise indexed LA area ( $P=0.001$ ). There were also trends for significantly higher resting and exercise E-wave velocity ( $P=0.10$  and  $P=0.07$ ) and exercise indexed LV end-systolic volume ( $P=0.07$ ).

### Determinants of Exercise SPAP and PHT

In simple linear regression, exercise SPAP was significantly correlated with resting SPAP ( $r=0.57$ ,  $P<0.0001$ ), heart rate ( $r=-0.20$ ,  $P=0.045$ ), E-wave velocity ( $r=0.19$ ,  $P=0.05$ ), exercise  $e'$ -wave velocity ( $r=0.19$ ,  $P=0.009$ ), and indexed LV end-diastolic volume ( $r=0.17$ ,  $P=0.044$ ). Both resting and exercise peak ( $r=0.23$ ,  $P=0.02$ ; and  $r=0.29$ ,  $P=0.003$ ) and mean ( $r=0.23$ ,  $P=0.016$ ; and  $r=0.24$ ,  $P=0.013$ ) transaortic pressure gradients were significantly correlated with exercise SPAP. In addition, the best correlation was found between exercise SPAP and exercise-induced changes in indexed LA area ( $r=0.40$ ,  $P<0.0001$ ). Multiple linear regression revealed that the independent predictors of exercise SPAP were exercise  $e'$ -wave velocity ( $\beta=11\pm5$ ;  $P=0.046$ ), exercise indexed LV end-diastolic volume ( $\beta=0.14\pm0.07$ ;  $P=0.038$ ), resting SPAP ( $\beta=0.9\pm0.2$ ;  $P<0.0001$ ), and exercise-induced changes in indexed LA area ( $\beta=1.3\pm0.4$ ;  $P=0.001$ ).

On multivariable analysis, with logistic regression (Table 3), the independent predictors of exercise PHT were male sex (odds ratio, 4.3;  $P=0.002$ ), resting SPAP (odds ratio, 1.16;  $P=0.002$ ), exercise indexed LV end-diastolic volume (odds ratio, 1.04;  $P=0.026$ ), exercise  $e'$ -wave velocity (odds ratio,

**Table 2. Resting and Exercise Echocardiographic Data**

Variables	Whole Cohort (n=105)	No Exercise PHT (n=47, 45%)	Exercise PHT (n=58, 55%)	P
<b>Resting LV function</b>				
Indexed LV end-systolic volume, mL/m <sup>2</sup>	19±10	19±9	20±11	0.64
Indexed LV end-diastolic volume, mL/m <sup>2</sup>	54±17	51±15	57±18	0.045
LV ejection fraction, %	67±7.6	66±7.5	67.5±7.7	0.40
LV global longitudinal strain, %	-16.3±2.6	-16.3±2.5	-16.2±2.7	0.82
E-wave velocity, cm/s	0.80±0.2	0.76±0.2	0.84±0.2	0.10
A-wave velocity, cm/s	0.93±0.3	0.89±0.3	0.97±0.3	0.23
e'-wave velocity, cm/s	7.8±2.2	7.6±1.8	8.0±2.5	0.35
E/A ratio	0.92±0.4	0.90±0.3	0.94±0.4	0.64
E/e' ratio	10.9±3.6	10.4±3.1	11.2±4.1	0.28
<b>Exercise LV function</b>				
Indexed LV end-systolic volume, mL/m <sup>2</sup>	18±8.3	17±7.3	20±8.9	0.07
Indexed LV end-diastolic volume, mL/m <sup>2</sup>	54±17	50±15	57±19	0.04
LV ejection fraction, %	67±9	67±8	66±10	0.41
E-wave velocity, cm/s	1.27±0.3	1.22±0.3	1.33±0.3	0.07
A-wave velocity, cm/s	1.01±0.3	0.98±0.3	1.05±0.3	0.43
e'-wave velocity, cm/s	10.1±2.7	9.2±2.1	10.8±3.0	0.004
E/A ratio	1.35±0.6	1.25±0.4	1.44±0.8	0.25
E/e' ratio	13.4±5.2	13.3±4.6	13.4±6.0	0.94
<b>Resting aortic stenosis severity</b>				
Peak transaortic gradient, mm Hg	72±23	67±19	76±26	0.046
Mean transaortic gradient, mm Hg	45±15	42±12	47±16	0.04
Aortic valve area, cm <sup>2</sup>	0.89±0.1	0.88±0.1	0.90±0.1	0.59
Indexed aortic valve area, cm/m <sup>2</sup>	0.50±0.1	0.49±0.1	0.50±0.1	0.63
<b>Exercise aortic stenosis severity</b>				
Peak transaortic gradient, mm Hg	91±28	83±21	97±31	0.008
Mean transaortic gradient, mm Hg	57±18	53±14	60±20	0.04
Aortic valve area, cm <sup>2</sup>	0.97±0.3	0.95±0.2	0.99±0.3	0.41
Indexed aortic valve area, cm/m <sup>2</sup>	0.54±0.16	0.53±0.1	0.55±0.2	0.46
Resting indexed LA area, cm <sup>2</sup> /m <sup>2</sup>	12.5±3.4	12.7±4	12.3±3	0.64
Exercise indexed LA area, cm <sup>2</sup> /m <sup>2</sup>	11.2±3.6	9.8±3.6	12.2±3.4	0.001
Resting PHT, n (%)	6 (6)	0 (0)	6 (10)	0.027
Resting SPAP, mm Hg	38±8	34±6	41±8	<0.0001
Exercise SPAP, mm Hg	62±16	48±9	74±9	<0.0001

PHT indicates pulmonary arterial hypertension; LV indicates left ventricular; LA, left atrial; and SPAP, systolic pulmonary arterial pressure.

1.35;  $P=0.047$ ), and exercise-induced changes in indexed LA area (odds ratio, 1.36;  $P=0.006$ ).

### Cardiac Event-Free Survival

The follow-up was complete in all patients (100%). The mean follow-up time was  $19\pm11$  months (median, 16 months; range, 2–48 months). During follow-up, 56 patients (53%) fulfilled the predefined end point, resulting in event-free survival of  $72\pm4\%$ ,  $50\pm5\%$ , and  $34\pm6\%$  at the 1-, 2-, and 3-year follow-up, respectively. There were 7 cardiovascular deaths during the follow-up (3 sudden deaths and 4 deaths after heart failure hospitalization). Of note, the 7 patients who died had developed exercise PHT (12%), but only 1 had resting PHT ( $P=0.014$ ). The remaining cardiac events were

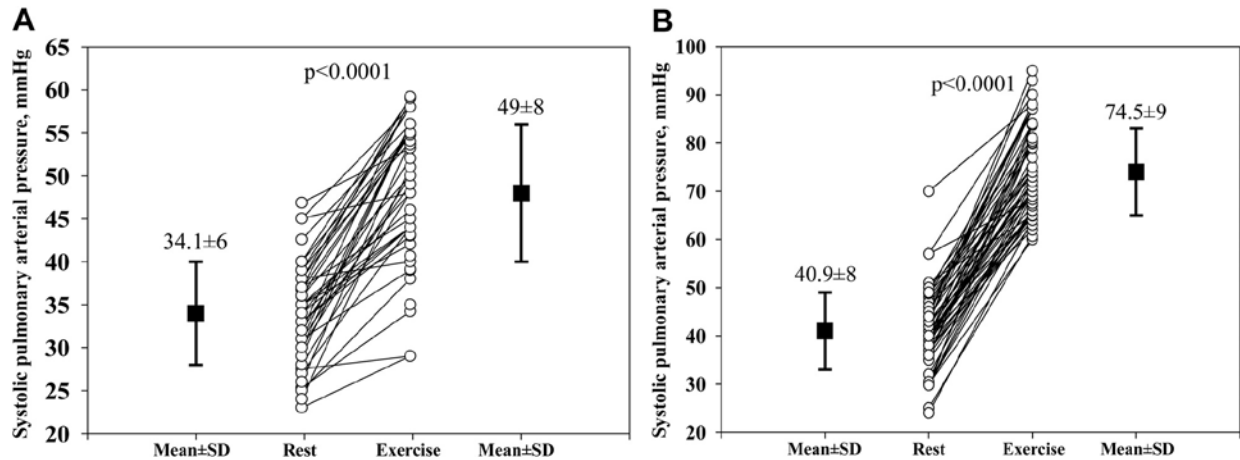
aortic valve replacement dictated by the onset of symptoms ( $n=49$ ). The main indication for surgery was the occurrence of syncope ( $n=4$ ), angina ( $n=6$ ), dyspnea ( $n=38$ ), and significant arrhythmia ( $n=1$ ).

During the follow-up, among the 6 patients with resting PHT, 1 died, 2 underwent an aortic valve replacement, and 3 remained free of event.

The raw rate of cardiac event (number of patients with an event divided by total number of patients in each group) was significantly higher in patients with exercise PHT ( $n=39$  versus  $n=17$ , 67% versus 36%;  $P=0.0015$ ).

Patients with exercise PHT had lower cardiac event-free survival (at 1 year,  $65\pm6\%$  versus  $81\pm6\%$ ; at 2 years,  $43\pm7\%$  versus  $59\pm8\%$ ; at 3 years,  $22\pm7\%$  versus  $55\pm9\%$ ;  $P=0.014$ ;





**Figure 1.** Impact of exercise on systolic pulmonary arterial pressure in patients without exercise pulmonary hypertension (A) and with exercise pulmonary hypertension (B).

Figure 2). In univariable analysis, exercise PHT was associated with 2-fold increase in cardiac events compared with patients without exercise PHT ( $P=0.017$ ; Table 4). Other univariable predictors of cardiac event were peak aortic jet velocity (hazard ratio [HR], 2; 95% confidence interval [CI], 1.35–2.97;  $P=0.001$ ), mean aortic transvalvular gradient (HR, 1.03; 95% CI, 1.01–1.04;  $P=0.02$ ), LV filling time (HR, 1.01; 95% CI, 1.00–1.01;  $P=0.014$ ), indexed LV end-systolic volume (HR, 1.03; 95% CI, 1.01–1.05;  $P=0.018$ ), indexed LV end-diastolic volume (HR, 1.02; 95% CI, 1.01–1.04;  $P=0.002$ ), and indexed LA area (HR, 1.06; 95% CI, 1.00–1.13;  $P=0.049$ ). Of note, exercise capacity, as assessed by the maximal reached METs, was not associated with reduced cardiac-event free survival (HR, 1.83; 95% CI, 0.7–4.8;  $P=0.21$ ), and none of the other exercise parameters was associated with outcome.

Resting PHT ( $n=6$ ) was not associated with reduced cardiac event-free survival ( $P=0.37$ ). However, there was a significant relationship between resting SPAP and outcome (HR, 1.03; 95% CI, 1.00–1.06;  $P=0.03$ ). This relationship remained significant after adjustment for age and sex (HR, 1.04; 95% CI, 1.00–1.07;  $P=0.03$ ) but not after adjustment for peak or mean aortic transvalvular gradient (HR, 1.03; 95% CI, 0.99–1.06;  $P=0.135$ ; and HR, 1.03; 95% CI, 0.99–1.06;  $P=0.08$ , respectively). Further adjustment with other resting echocardiographic data led

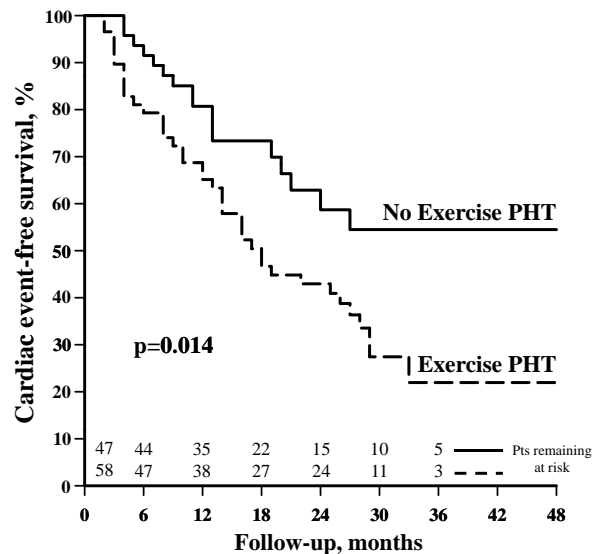
to a definite nonsignificant association between resting SPAP and cardiac event-free survival (HR, 1.03; 95% CI, 0.99–1.07;  $P=0.15$ ).

After adjustment for age and sex, exercise PHT was independently associated with reduced cardiac event-free survival (HR, 1.9; 95% CI, 1.1–3.4;  $P=0.025$ ; Table 4). With further adjustment including resting echocardiographic data, exercise PHT remained independently associated with cardiac events (HR, 1.8; 95% CI, 1.0–3.3;  $P=0.047$ ). As previously reported, exercise-induced changes in mean transaortic pressure gradient were associated with reduced event-free survival (HR, 1.02; 95% CI, 1.01–1.03;  $P=0.003$ ). In the multivariable model (Table 4), after adjustment for age, sex, resting echocardiographic data, and exercise-induced changes in mean transvalvular pressure gradient, exercise PHT remained an independent predictor of high risk of cardiac events (HR, 2.0; 95% CI, 1.1–3.6;  $P=0.025$ ). Of note, in this multivariable model, exercise-induced change in mean transaortic pressure gradient was also an independent predictor of events ( $P=0.043$ ).

**Table 3. Logistic Regression: Independent Determinants of Exercise Pulmonary Arterial Hypertension**

Variables	Odds Ratio	95% CI	P
Male sex	4.3	1.2–15.1	0.002
Resting SPAP (per mm Hg)	1.16	1.06–1.27	0.002
Exercise indexed LV end-diastolic volume (per mL/m <sup>2</sup> )	1.04	1.00–1.07	0.026
Exercise-induced changes in indexed LA area (per cm <sup>2</sup> /m <sup>2</sup> )	1.36	1.1–1.7	0.006
Exercise e'-wave velocity (per cm/s)	1.35	1.00–1.8	0.047

CI indicates confidence interval; SPAP, systolic pulmonary arterial pressure; LV, left ventricular; and LA, left atrial. Adjustment performed with age, resting heart rate, resting mean transaortic pressure gradient, exercise peak transaortic pressure gradient, exercise e'-wave velocity, and exercise indexed LV end-systolic volume.



**Figure 2.** Cardiac event-free survival according to the presence or absence of exercise pulmonary hypertension (PHT).

**Table 4. Cox Proportional Hazards Regression Analysis for the Prediction of Cardiac Event-Free Survival**

Models	Exercise PHT		
	Hazard Ratio	95% CI	P
Univariable	2.0	1.1–3.5	0.017
Age and sex adjusted	1.9	1.1–3.4	0.025
Resting data adjusted*	1.8	1.1–3.3	0.045
Exercise data adjusted†	2.0	1.1–3.6	0.025

PHT indicates pulmonary arterial hypertension; CI, confidence interval.

\*Adjustment including age, sex, indexed left atrial area, left ventricular end-systolic volume, left ventricular end-diastolic volume, E/e' ratio, and peak aortic jet velocity.

†Adjustment including age, sex, resting echocardiographic data, and exercise-induced changes in mean transaortic pressure gradient.

Using receiver-operating characteristic curve analysis, we found that exercise SPAP had a good accuracy for predicting cardiac events (area under the curve, 0.69). Of interest, the best cutoff value to predict cardiac events was exercise SPAP >60 mm Hg: sensitivity, 70%; specificity, 62%; positive predictive value, 67%; and negative predictive value, 64%.

In addition, to assess whether exercise SPAP was more accurate than resting SPAP in predicting cardiac events, we generated the C statistic for each model. The C statistics were systematically higher with exercise SPAP than resting SPAP in univariate age- and sex-adjusted or age-, sex-, and resting echocardiographic data-adjusted models (0.610 versus 0.515, 0.613 versus 0.557, and 0.664 versus 0.611, respectively).

### Incremental Prognostic Value of Exercise PHT Over Resting AS Severity

In the whole multivariate model, peak aortic jet velocity was the strongest resting echocardiographic predictor of outcome (HR, 1.02; 95% CI, 1.01–1.03;  $P<0.0001$ ). Figure 3 shows the incremental value of exercise PHT over markedly elevated peak aortic jet velocity (>4.0 m/s) in the prediction of cardiac events. The combination of high peak aortic jet velocity and exercise PHT resulted in the worse outcome ( $P=0.008$ ). Compared with the whole cohort, patients with high peak aortic jet

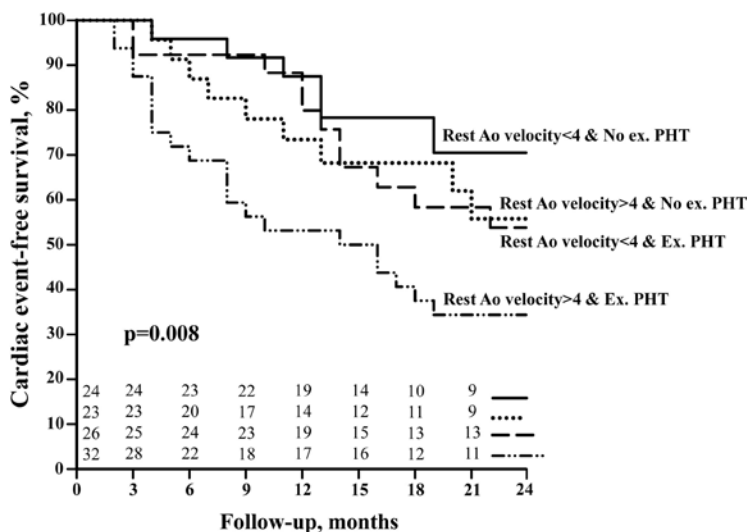
velocity and exercise PHT had a 2.4-fold increased risk of reduced event-free survival (95% CI, 1.4–4.03;  $P=0.002$ ). Reducing the analysis only to the subset of patients with markedly elevated peak aortic jet velocity resulted in a significant impact of exercise PHT on outcome (HR, 2.4; 95% CI, 1.1–5.2;  $P=0.014$ ). Of note, patients with exercise PHT but without markedly elevated peak aortic jet velocity had a 2-year event-free survival ( $54\pm 10\%$  versus  $56\pm 11\%$ ;  $P=0.77$ ) similar to that of patients with markedly elevated peak aortic jet velocity but without exercise PHT. Furthermore, the 7 deaths occurring during the follow-up were in patients with both markedly elevated peak aortic jet velocity and exercise PHT ( $P=0.001$ ).

### Discussion

The main findings of the present study are that (1) exercise PHT (ie, exercise SPAP >60 mm Hg) is a frequent condition (55% of the cohort) in patients with asymptomatic severe AS and preserved LVEF; (2) the independent determinants of exercise PHT are male sex, resting SPAP, and exercise parameters of diastolic burden (exercise indexed LV end-diastolic volume, exercise e'-wave velocity, and exercise-induced changes in indexed LA area); (3) exercise PHT is associated with an alarming rate of cardiac death (12%) and with significant reduced cardiac event-free survival; (4) exercise PHT doubles the risk of cardiac events independently of age, sex, resting echocardiographic data, and exercise-induced changes in mean transaortic pressure gradient; and (5) exercise PHT had an incremental prognostic value compared with resting AS severity parameter. Conversely, although resting elevated SPAP may affect clinical outcome, its prognostic value was weak in our study.

### Pulmonary Arterial Hypertension in AS

The prevalence of PHT varies considerably over studies according to patient selection criteria and the threshold used to define PHT. Overall, an SPAP >50 mm Hg is found in 15% to 30% of patients with severe AS,<sup>16–18</sup> and recently, severe SPAP (>60 mmHg) was reported in 19% of a large cohort of 626 AS patients.<sup>19</sup>



**Figure 3.** Cardiac event-free survival according to the presence or absence of exercise pulmonary hypertension (Ex. PHT) and markedly elevated peak aortic (Ao) jet velocity (>4 m/s).

However, to the best of our knowledge, no study has reported the prevalence of PHT in truly asymptomatic patients. In our cohort, an SPAP >50 mm Hg was rare and identified in only 6 patients (6%), suggesting that the impact of severe AS on LV diastolic function<sup>20</sup> and LA geometry and function<sup>21,22</sup> may be generally well counterbalanced by LA compliance and/or pulmonary vascular resistance. Of interest, these patients with resting PHT were particularly old and had very severe AS, and half of them experienced cardiac events (including 1 death and 2 aortic valve replacement), suggesting the poor outcome of this subset. In contrast, a recent study has shown that PHT is frequent in surgery-referred patients with LV dysfunction and is independently associated with LA function impairment.<sup>23</sup>

The potential impact on outcome of PHT in patients with AS is also a source of debate. In 1979, McHenry et al<sup>7</sup> showed that PHT could be considered a harbinger for sudden death and clinical deterioration. More recently, PHT in severe AS was also associated with a dismal prognosis under conservative management.<sup>24,25</sup> Nevertheless, PHT may frequently and rapidly be abolished after aortic valve replacement,<sup>24–26</sup> leading to a more favorable long-term outcome.<sup>27</sup>

### Exercise PHT in AS

Exercise PHT was significantly more frequent (55%) than resting PHT (6%) in our cohort. This entity is characterized by lower resting heart rate and higher resting and peak exercise indexed LV end-diastolic volume. During exercise, whereas some patients with no exercise PHT may have only a mild increase in SPAP (Figure 1A), the vast majority of those with exercise PHT (Figure 1B) experienced a marked rise in SPAP. This phenomenon is essentially determined by the level of exercise  $e'$ -wave velocity, the exercise indexed LV end-diastolic volume, and the exercise-induced changes in indexed LA area.

In AS, the chronically increased afterload results in progressive LV remodeling and myocardial hypertrophy. Although the increase in LV wall thickness is a compensatory mechanism that reduces systolic wall stress, it can result in impaired LV relaxation, reduced LV compliance, and increased metabolic demands. The ability of the LV to adequately fill under normal pressures is thus altered and the LV diastolic pressure increases. As a result, LA slowly expands and becomes dysfunctional and less compliant, making it impossible to limit the transmission to the pulmonary vascular bed of any further increase, even minimal, in LV end-diastolic pressure observed during exercise. Furthermore, any degree of LV diastolic dysfunction (relaxation abnormality) and increased LV filling pressure at rest and/or at exercise can be sufficient to trigger exercise PHT. In these patients, exercise echocardiography enables us to unmask a more advanced impairment in LV diastolic properties, namely latent LV diastolic dysfunction. This is line with our observations because exercise PHT was related mainly to exercise parameters of diastolic burden. Of note, a limitation in LA compliance was confirmed by the significant correlation observed between exercise-induced changes in indexed LA area and exercise SPAP. For a given increase in LV filling pressure, patients with limited changes in LA dimensions (ie, exhausted LA compliance reserve) during exercise displayed a higher

increase in SPAP; this is even truer if LA emptying is not facilitated any more from recruitable LA function.

### Clinical Implications

Our results are the first to demonstrate that the measurement of SPAP during exercise echocardiography may improve risk stratification of asymptomatic severe AS. Indeed, patients who experienced exercise PHT (SPAP >60 mm Hg) multiplied by 2 the risk of cardiac events, even after adjustment for demographic and resting and exercise echocardiographic data. Among the 7 cardiovascular-related deaths that occurred during follow-up, only 1 patient had resting PHT, but all of those patients had developed exercise PHT. Of interest, our data show that resting elevated SPAP is not independently associated with reduced cardiac event-free survival in “truly” asymptomatic patients with severe AS.

Hence, these results strongly emphasize the usefulness of exercise stress echocardiography in this clinical situation. Exercise PHT also had incremental prognostic value compared with AS severity parameters (ie, aortic jet velocity). Indeed, in patients with markedly elevated aortic jet velocity, those with exercise PHT exhibited a significant lower cardiac event-free survival (Figure 3) compared with the others, resulting in poorer outcome. Furthermore, patients with exercise PHT but without markedly elevated aortic jet velocity had a prognosis similar to that for those without exercise PHT but with high aortic jet velocity. Thus, in patients with asymptomatic AS and <4-m/s aortic jet velocity, the presence of exercise PHT is still able to identify a subset of patients at dismal prognosis (Figure 3) who may require a closer follow-up to look for any changes in LV diastolic function and symptoms.

During tests, an exercise-induced increase in mean transaortic pressure gradient by >18 to 20 mm Hg has recently been identified as a marker of poor prognosis in asymptomatic AS.<sup>28,29</sup> Our results confirm that this parameter is associated with reduced cardiac event-free survival, but we further show that exercise PHT is an predictor of impaired prognosis independently of the changes in LV afterload. Interestingly, only one third of patients with exercise PHT also had a marked increase in mean transaortic pressure gradient. This suggests that the presence of elevated exercise SPAP may unmask a subset of asymptomatic patients with latent LV diastolic dysfunction, reduced atrioventricular compliance, and impaired pulmonary vascular resistance. These patients are probably more subject to rapidly developing symptoms and seem to be at higher risk of cardiac-related death. Consequently, the use of exercise stress echocardiography in asymptomatic patients with severe AS could be recommended. At peak exercise, the measurement of both mean transaortic pressure gradient and SPAP, which are technically easy and rapid and have good reproducibility,<sup>13,29–32</sup> may improve the management of such patients. Indeed, the high rate of cardiac-related death observed in patients with exercise PHT (12%), despite normal exercise tests, should encourage prompt surgery, which is, in asymptomatic patients, associated with very low operative mortality<sup>3</sup> and low prosthesis-related complication rate. Conversely, patients with no exercise PHT and no marked increase in mean transaortic gradient can be followed up safely.

## Limitations

Apparent nonsignificant results may be related to the relatively small sample size of the study. Specifically, the absence of relationship between maximal exercise capacity parameters and cardiac event-free survival could be due mainly to a type II error. Nevertheless, this limitation does not affect the validity of the main result of the study, which is the demonstration that exercise PHT may have an incremental prognostic value in patients with asymptomatic severe AS.

Despite careful assessment, the evaluation of the occurrence of symptoms at a low workload during exercise remains subjective. Hence, although rare, it is possible that some patients with symptoms during exertion were included in the final population.

As in our previous studies,<sup>13,33</sup> the right atrial pressure was estimated at 10 mm Hg both at rest and during exercise. Hence, we may have missed the potential influence of exercise-induced changes in right atrial pressure. Nevertheless, the noninvasive evaluation of right atrial pressure during exercise (ie, when venous compliance is known to decrease) with noninvasive methods such as Doppler echocardiography remains difficult, is probably subject to low accuracy, and is not validated. Moreover, right atrial pressure is frequently assumed to be 5 mm Hg in normal subjects<sup>30</sup> and 10 mm Hg in patients with valvular disease.<sup>12</sup>

The absence of evaluation of the presence and extent of coronary artery disease in patients not referred to surgery is also a limitation of this report. However, these patients have, by definition, no resting symptoms and normal LVEF and exercise test, suggesting that they are truly asymptomatic. In this context, coronary angiography is not recommended, and the rate of significant coronary artery disease in our population is probably low.

## Conclusions

In asymptomatic patients with severe AS, the main determinants of exercise PHT are male sex, resting SPAP, and exercise parameters of diastolic burden. Exercise PHT is associated with a 2-fold increased risk of cardiac events and provides incremental prognostic value independently of demographic, resting echocardiographic data, and exercise-induced changes in mean transaortic pressure gradient. These results support the use of exercise stress echocardiography in asymptomatic AS.

## Acknowledgments

We thank M. Carmine Celentano for excellent technical assistance.

## Sources of Funding

Dr Magne is research associate from the F.R.S-FNRS, Brussels, Belgium, and received grants from the Fonds Léon Fredericq, Liège, Belgium, and from the Fond pour la Chirurgie Cardiaque, Belgium.

## Disclosures

None.

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### CLINICAL PERSPECTIVE

The management and timing of surgery in asymptomatic patients with severe aortic stenosis remain matters of concern. The risks of aortic valve surgery and late complications of prosthesis in such patients need to be balanced against the possible prevention of sudden death and lowering of cardiac mortality. Hence, early elective surgery could be proposed only to well-selected patients considered at high risk of poor outcome. In the present study, 105 consecutive asymptomatic patients with severe aortic stenosis underwent comprehensive resting and exercise stress echocardiography to evaluate the presence of pulmonary hypertension (PHT). The results showed that 55% of asymptomatic patients may develop exercise PHT. Patients with exercise PHT had significantly lower cardiac event-free survival and a markedly higher rate of death than those without exercise PHT. In addition, exercise PHT was associated with poorer outcome independently of demographic and resting echocardiographic data and exercise-induced changes in mean transaortic pressure gradient. Beyond both resting aortic stenosis severity and systolic pulmonary arterial pressure, the assessment of the presence of exercise PHT provided important incremental predictive value. Even in patients with markedly elevated aortic jet velocity, those with exercise PHT depicted a higher risk of reduced cardiac event-free survival. These results strongly support the use of exercise stress echocardiography in the management of asymptomatic severe aortic stenosis. Early elective aortic valve surgery to prevent irreversible left ventricular myocardial damage, diastolic dysfunction, and symptoms could be advised in patients developing exercise PHT. In contrast, asymptomatic patients with no exercise PHT may be conservatively followed up.